Migraine headache

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Luis E Morillo

QUESTIONS

INTERVENTIONS

Key Messages

- **Eletriptan** One systematic review and subsequent RCTs have found that eletriptan increases headache relief at 2 hours compared with placebo. One systematic review and subsequent RCTs have found that eletriptan 40 and 80 mg increases headache relief at 2 hours compared with sumatriptan 50 and 100 mg. One RCT found that eletriptan 40 and 80 mg increased headache relief at 2 hours compared with ergotamine plus caffeine.
- **Ibuprofen** Five RCTs have found that ibuprofen improves migraine symptoms compared with placebo.
- **Naratriptan** One systematic review and subsequent RCTs have found that naratriptan increases headache relief at 2 hours compared with placebo. One systematic review has found that sumatriptan 100 mg increases headache relief at 2 hours compared with naratriptan 2.5 mg. However, one subsequent RCT found no significant difference in headache recurrence. One RCT found no significant difference between naratriptan 2.5 mg and zolmitriptan 2.5 mg in headache relief at 4 hours. One RCT identified by a systematic review found that naratriptal reduced headache relief at 2 hours compared with rizatriptan.
- **Rizatriptan** One systematic review and subsequent RCTs have found that rizatriptan improves headache relief compared with placebo. Two RCTs found no significant difference between rizatriptan and zolmitriptan in headache relief at 2 hours. One RCT identified by a systematic review found that rizatriptan increased headache relief at 2 hours compared with naratriptan. One RCT found that rizatriptan increased headache relief and reduced nausea and vomiting at 2 hours compared with ergotamine plus caffeine.
- **Salicylates** RCTs have found that oral or intravenous salicylates (alone or in combination with metoclopramide, paracetamol, or caffeine) increase headache relief compared with placebo. One RCT found no significant difference between aspirin and paracetamol plus codeine in headache relief. One RCT

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found no significant difference between aspirin plus metoclopramide and sumatriptan in headache relief. One RCT found that oral lysine acetylsalicylate plus metoclopramide increased headache relief and reduced nausea and vomiting at 2 hours compared with ergotamine plus caffeine. One RCT found no significant difference in headache relief between aspirin plus metoclopramide and zolmitriptan.

- **Sumatriptan** Systematic reviews and subsequent RCTs have found that subcutaneous, oral, or intranasal sumatriptan increases headache relief compared with placebo. RCTs found no significant difference in headache relief between sumatriptan and aspirin plus metoclopramide, tolfenamic acid, or zolmitriptan. RCTs have found that oral or nasal sumatriptan increase headache relief compared with oral or nasal ergotamine. One systematic review has found that sumatriptan 100 mg increases headache relief at 2 hours compared with naratriptan 2.5 mg. However, one subsequent RCT found no significant difference in headache recurrence. One systematic review and subsequent RCTs have found that eletriptan 40 and 80 mg increases headache relief at 2 hours compared with sumatriptan 50 and 100 mg.
- **Zolmitriptan** One systematic review and two subsequent RCTs have found that oral zolmitriptan increases headache relief compared with placebo. One systematic review and two subsequent RCTs found no significant difference between zolmitriptan and sumatriptan in headache relief. One RCT found no significant difference in headache relief between aspirin plus metoclopramide and zolmitriptan. One RCT found no significant difference between naratriptan 2.5 mg and zolmitriptan 2.5 mg in headache relief at 4 hours.
- **Diclofenac** RCTs have found that oral or intramuscular diclofenac improves headache symptoms compared with placebo. One RCT found that intramuscular diclofenac improved migraine symptoms compared with intramuscular paracetamol.
- **Ergotamine** One systematic review found limited evidence from four RCTs that ergotamine (with or without caffeine) improved headache relief compared with placebo. One overview of harms suggested that ergotamine increased nausea and vomiting compared with placebo. RCTs have found that ergotamine (or its derivatives, with or without caffeine and cyclizine) is less effective for migraine symptoms than sumatriptan. They found limited evidence that it was less effective than naproxen. RCTs found that thalergotarine plus caffeine reduced headache relief and increase nausea and vomiting at 2 hours compared with oral lysine acetylsalicylate plus metoclopramide and rizatriptan.
- **Naproxen** Three small RCTs found that naproxen reduced migraine symptoms compared with placebo. Two RCTs found that naproxen reduced symptoms compared with ergotamine (with or without caffeine plus cyclizine). However, one further RCT found no significant difference between naproxen and ergotamine in pain relief after 1 hour.
- **Tolfenamic acid** RCTs found limited evidence that tolfenamic acid improved duration and severity of headache compared with placebo. RCTs found no significant difference in symptom relief between tolfenamic acid and sumatriptan or paracetamol.

DEFINITION Migraine is a primary headache disorder manifesting as recurring attacks usually lasting for 4–72 hours and involving pain of moderate to severe intensity, often with nausea, sometimes vomiting, and/or sensitivity to light, sound, and other sensory stimuli. The 1988 International Headache Society criteria (see glossary,

p 1837) include separate criteria for migraine with and migraine without associated aura.[1] Unless stated otherwise, RCTs used International Headache Society criteria for migraine with or without aura.

INCIDENCE/ PREVALENCE Migraine is common worldwide. Prevalence has been reported to be 5–25% in women and 2–10% in men. Overall, the highest incidence for migraine without aura has been reported between the ages of 10 and 11 years (10/1000 person years). The peak incidence of migraine without aura in males is between ages 10 and 11 years (10/1000 person years) and in females between ages 14 and 17 years (19/1000 person years).[2] The incidence of migraine with aura peaks in males at age 5 years (7/1000 person years) and in females at age 12–13 years (14/1000 person years).[2] Female prevalence of migraine with or without aura has a declining trend after age 45–50 years.

AETIOLOGY/ RISK FACTORS Data from independent representative samples from Canada,[3,4] the USA,[5,6] several countries in Latin America,[7] and several countries in Europe,[8–11] Hong Kong,[12] and Japan[13] show a female to male predominance and a peak in middle aged women. Migraine has been reported to be 50% more likely in people with a family history of migraine.[14]

PROGNOSIS Acute migraine is self limiting and only rarely results in permanent neurological complications. Chronic recurrent migraine may cause disability through pain, and may affect daily functioning and quality of life.

AIMS OF INTERVENTION To reduce frequency of migraine, intensity of accompanying symptoms, and duration of headache, with minimal adverse effects.

OUTCOMES Headache relief or being pain free (see glossary, p 1838) at different times after medication. Pain relief at specific post-dose times. In this review, headache relief is reported at 2 hours unless otherwise stated. Some RCTs include the need for rescue medication and headache recurrence (see glossary, p 1837) as outcome measures.

METHODS *Clinical Evidence* search and appraisal August 2003.

QUESTION What are the effects of drug treatments for acute migraine?

OPTION SALICYLATES

RCTs have found that oral or intravenous salicylates (alone or in combination with metoclopramide, paracetamol, or caffeine) increase headache relief compared with placebo. One RCT found no significant difference between aspirin and paracetamol plus codeine in headache relief. One RCT found no significant difference between aspirin plus metoclopramide and sumatriptan in headache relief. One RCT found that oral lysine acetylsalicylate plus metoclopramide increased headache relief and reduced nausea and vomiting at 2 hours compared with ergotamine plus caffeine. One RCT found no significant difference in headache relief between aspirin plus metoclopramide and zolmitriptan.

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Benefits: We found no systematic review but found 12 RCTs.[15–26] **Oral lysine acetylsalicylate (L-ASA):** One RCT (266 people, 475 migraine attacks) found that oral L-ASA 1620 mg plus metoclopramide 10 mg significantly increased headache relief (see glossary, p 1837) compared with placebo (AR 56% with L-ASA *v* 28% with placebo; RR 2.0, 95% CI 1.6 to 2.5).[15] A second RCT compared three treatments: oral L-ASA 1620 mg plus metoclopramide 10 mg, oral sumatriptan 100 mg, and placebo.[16] It found that L-ASA plus metoclopramide significantly increased headache relief compared with placebo (AR 57% with L-ASA *v* 24% with placebo; RR 2.4, 95% CI 1.7 to 3.3). The difference between active treatment groups was not significant (AR 57% with L-ASA *v* 54% with sumatriptan; P = 0.50). **Intravenous L-ASA:** One RCT (278 people) compared three treatments: L-ASA 1800 mg intravenously, sumatriptan 6 mg subcutaneously, and placebo.[17] It found that both L-ASA and sumatriptan significantly increased headache relief compared with placebo, and that sumatriptan significantly increased headache relief compared with L-ASA (AR 74% with L-ASA *v* 91% with sumatriptan *v* 24% with placebo; RR for L-ASA *v* placebo 3.1, 95% CI 1.8 to 5.4; RR for L-ASA *v* sumatriptan 0.8, 95% CI 0.7 to 0.9). A second, smaller, crossover RCT (112 attacks in 56 people) compared L-ASA 1000 mg intravenously versus ergotamine 0.5 mg subcutaneously.[18] It found no significant difference between groups in pain intensity score on a visual analogue scale. **Effervescent aspirin:** One crossover RCT (120 people) compared effervescent aspirin 650 mg with and without metoclopramide 10 mg versus placebo.[19] At 2 hours aspirin with or without metoclopramide reduced headache significantly more than placebo (P < 0.001). A second RCT (374 people) compared effervescent aspirin 1000 mg versus placebo.[20] It found that aspirin significantly increased headache relief compared with placebo (AR 55% with aspirin *v* 37% with placebo; RR 1.5, 95% CI 1.2 to 1.9). **Dispersible aspirin:** One crossover RCT (101 people with migraine, 73 of whom received both treatments) compared mouth dispersible aspirin 900 mg versus placebo in two consecutive attacks.[21] It found that aspirin significantly increased headache relief at 2 hours compared with placebo, and significantly reduced need for rescue medication (see glossary, p 1838) (AR for headache relief 48% with aspirin *v* 19% with placebo; P = 0.0005; difference in need for rescue medication: P < 0.01). **Other combinations:** One large RCT (1357 people with non-disabling migraine) compared oral paracetamol 250 mg plus aspirin 250 mg plus caffeine 65 mg versus placebo.[22] Combination treatment improved headache relief compared with placebo (AR 59% with combination *v* 33% with placebo; RR 1.8, 95% CI 1.6 to 2.1). A second, crossover RCT (198 people treated for 3 consecutive migraine attacks) found no significant difference in headache relief between aspirin 1000 mg orally and paracetamol 400 mg plus codeine 25 mg.[23] However, both improved headache relief compared with placebo (P = 0.0003 with aspirin and P = 0.0002 with paracetamol plus codeine). **Aspirin versus sumatriptan:** One RCT (358 people) found no significant difference between oral aspirin 900 mg plus metoclopramide 10 mg and oral sumatriptan 100 mg in headache relief at 2 hours (AR 45% with

aspirin plus metoclopramide *v* 56% with sumatriptan; P = 0.078).[24] **Aspirin versus tolfenamic acid:** See benefits of tolfenamic acid, p 1824. **Aspirin versus zolmitriptan:** See benefits of zolmitriptan, p 1835. **Aspirin versus ergotamine:** See benefits of ergotamine, p 1825.

Harms: One RCT reported adverse effects related to L-ASA in 2%, to sumatriptan in 15%, and to placebo in 2% of people treated.[17] In this trial, severe harms were related to L-ASA in 3%, to sumatriptan in 5%, and to placebo in 2% of people treated. Another trial reported premature withdrawal of treatment in 1% with L-ASA, 3% with sumatriptan, and 2% with placebo.[16] The most frequently reported harms for L-ASA were somnolence, abdominal pain, nausea or vomiting, fatigue, and headache. The RCT comparing the combination of paracetamol, aspirin, and caffeine versus placebo reported no serious adverse effects.[22] **Versus zolmitriptan:** See harms of zolmitriptan, p 1836. **Versus ergotamine:** See harms of ergotamine, p 1827.

Comment: None.

OPTION DICLOFENAC

RCTs have found that oral or intramuscular diclofenac improves headache symptoms compared with placebo. One RCT found that intramuscular diclofenac improved migraine symptoms compared with intramuscular paracetamol.

Benefits: We found no systematic review. **Versus placebo:** We found three RCTs of oral diclofenac[27,28,30] and one RCT of intramuscular diclofenac.[29] The first RCT (170 people) found that diclofenac improved treatment success compared with placebo (success defined at 2 hours as a visual analogue scale score < 10 mm or headache duration of < 2 hours without need for rescue medication (see glossary, p 1838) within this period: AR 27% with diclofenac *v* 19% with placebo; RR 1.5, 95% CI 1.0 to 2.2).[27] The second RCT (72 people) found that diclofenac 50 or 100 mg significantly increased headache relief (see glossary, p 1837) compared with placebo (AR 39% with 50 mg *v* 44% with 100 mg *v* 22% with placebo; RR diclofenac 50 mg *v* placebo 1.8, 95% CI 1.0 to 3.1; RR diclofenac 100 mg *v* placebo 1.9, 95% CI 1.1 to 3.3).[28] The RCT found no significant difference between 50 mg and 100 mg doses of diclofenac. However, it found that diclofenac 100 mg significantly reduced need for rescue medication compared with placebo (AR 37% with diclofenac *v* 58% with placebo; RR 0.64, 95% CI 0.44 to 0.93). The third RCT (120 people with migraine with or without aura) compared intramuscular diclofenac 75 mg versus placebo.[29] At 1 hour, it found that diclofenac improved headache relief and reduced need for rescue medication compared with placebo in people with and without aura (headache relief in people without aura: AR 43.3% with diclofenac *v* 16.7% with placebo; P < 0.01; headache relief in people with aura: AR 50% with diclofenac *v* 13.3% with placebo; P < 0.01; rescue medication in people without aura: 20% with diclofenac *v* 50% with placebo; P < 0.05; rescue medication in people with aura: 11% with

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diclofenac *v* 42% with placebo; P < 0.05). The fourth RCT (156 people meeting International Headache Society criteria (see glossary, p 1837) for migraine with or without aura) compared three treatments: diclofenac potassium 50 or 100 mg, oral sumatriptan 100 mg, and placebo.[30] The trial found that diclofenac significantly reduced headache pain (measured on a visual analogue scale) at 2 hours compared with placebo (P < 0.001). **Versus sumatriptan:** The RCT comparing diclofenac, sumatriptan, and placebo found no significant difference between either dose of diclofenac and sumatriptan.[30] **Versus paracetamol:** One RCT (86 people) compared intramuscular diclofenac 75 mg versus intramuscular paracetamol in people with paroxysmal headaches accompanied by at least two of the following features: unilateral pain, nausea, visual and limb symptoms, and positive family history.[31] The trial found that diclofenac increased the proportion of people with partial relief of overall migraine symptoms (intensity and duration) within 35 minutes compared with paracetamol (AR 89% with diclofenac *v* 17% with paracetamol; RR 4.9, 95% CI 2.5 to 9.8).

Harms: In one RCT (72 people), 33% of people reported one or more adverse effects during one or more attacks.[28] Most adverse effects were rated as mild or moderate (gastrointestinal complaints were the most common, followed by tiredness and fatigue), but 12% of people rated adverse experiences as severe. In another RCT (170 people), 14% of people reported at least one adverse effect, with gastrointestinal effects being the most common (50%).[27] Only three people withdrew because of gastrointestinal symptoms. See non-steroidal anti-inflammatory drugs, p 1700.

Comment: None.

OPTION IBUPROFEN

Five RCTs have found that ibuprofen improves migraine symptoms compared with placebo.

Benefits: **Versus placebo:** We found no systematic review but found five RCTs comparing ibuprofen versus placebo.[32–36] The first RCT (729 people) found that oral ibuprofen (400 and 600 mg in gel formulation) significantly improved headache relief (see glossary, p 1837) compared with placebo (AR 72% with 400 mg *v* 72% with 600 mg *v* 50% with placebo; ibuprofen 400 mg *v* placebo RR 1.4, 95% CI 1.2 to 1.7; ibuprofen 600 mg *v* placebo RR 1.4, 95% CI 1.2 to 1.7).[32] It found no significant difference in the need for rescue medication (see glossary, p 1838). The second RCT (25 people, 146 migraines) found that ibuprofen significantly improved migraine index (see glossary, p 1838) (25 with ibuprofen *v* 46 with placebo; P = 0.0014) and reduced the need for rescue medication 4 hours after treatment (26% with ibuprofen *v* 56% with placebo; P = 0.007) compared with placebo.[33] The third RCT (40 people with common and classic migraine, 345 migraines) compared ibuprofen 800–1200 mg orally versus placebo.[34] The trial found that significantly more attacks were rated as mild with ibuprofen compared with placebo (P < 0.001) and significantly fewer attacks were rated as moderate (P < 0.05) or severe (P < 0.05). It also

found that ibuprofen reduced the need for rescue medication compared with placebo (AR 22% with ibuprofen *v* 81% with placebo; RR 0.27, 95% CI 0.20 to 0.36). One RCT (660 people with headache intensity (see glossary, p 1837) not requiring bed rest or inhibiting daily activities in more than 50% of attacks) compared ibuprofen 200 or 400 mg versus placebo with a follow up of 6 hours.[35] It found that ibuprofen significantly increased headache relief at 2 hours compared with placebo (AR 41.7% with ibuprofen 400 mg *v* 40.8% with ibuprofen 200 mg *v* 28.1% with placebo; P = 0.006 for both doses *v* placebo). The fifth RCT (40 people) compared an ibuprofen arginine preparation (400 mg orally) versus placebo.[36] It found that more people taking ibuprofen arginine versus placebo achieved "considerable" or "complete" relief within 2 hours (51% with ibuprofen *v* 7% with placebo; P < 0.01). Fewer people taking ibuprofen arginine received rescue medication (31% with ibuprofen *v* 48% with placebo) but no statistical analysis was performed.

Harms: One RCT did not report adverse effects.[34] Another RCT reported pain and stomach discomfort in 12% of people on treatment, which was not considered serious.[33] Another reported no significant difference in adverse events among treatment groups, and no serious adverse events.[35] See non-steroidal anti-inflammatory drugs, p 1700.

Comment: None.

OPTION NAPROXEN

Three small RCTs found that naproxen reduced migraine symptoms compared with placebo. Two RCTs found that naproxen reduced symptoms compared with ergotamine (with or without caffeine plus cyclizine). However, one further RCT found no significant difference between naproxen and ergotamine in pain relief after 1 hour.

Benefits: We found no systematic review. **Versus placebo:** We found one crossover RCT (37 people with classic or common migraine) comparing oral naproxen 750–1250 mg versus placebo.[37] It found that naproxen significantly reduced headache intensity (see glossary, p 1837) (P = 0.047). However, it found no significant difference in need for rescue medication (see glossary, p 1838) (absolute numbers not reported; P = 0.13). A second crossover RCT (40 people with common or classic migraine) comparing naproxen 750–1000 mg versus placebo found that naproxen reduced overall pain intensity (rated as mild, moderate, or severe; P = 0.011; time of evaluation not reported).[38] The need for rescue medication after 2 hours was also significantly lower for naproxen (AR 47% with naproxen *v* 72% with placebo; P = 0.002; insufficient data for calculation of RR). A third RCT compared three treatments: naproxen, ergotamine (plus caffeine plus cyclizine), and placebo.[39] It found that naproxen significantly increased pain relief compared with ergotamine at 1 hour after the first dose (P = 0.032). **Versus ergotamine:** We found three RCTs, which compared oral naproxen 750–1750 mg versus ergotamine 2–4 mg alone or with caffeine 91.5 mg plus cyclizine chlorhydrate 50 mg.[39–41] The first RCT (114

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people) found that naproxen significantly reduced migraine intensity (rated as mild, moderate, severe, or incapacitating) compared with ergotamine plus caffeine plus cyclizine (P = 0.014). However, it found no significant difference in need for rescue medication.[39] The second RCT (37 people with classic or common migraine) compared naproxen versus ergotamine.[40] In this trial, 47% of people were reported to have terminated the study prematurely. The trial found that naproxen significantly reduced migraine intensity (rated as none, mild, moderate, or severe) compared with ergotamine (P = 0.04). However, it found no significant difference in need for rescue medication (23% with naproxen *v* 29% with ergotamine). The third RCT (41 people) compared three treatments: naproxen, ergotamine, and placebo.[41] It found no significant difference in pain relief at 1 hour after the first dose between naproxen and ergotamine (P = 0.65).

Harms: In one RCT, adverse effects were reported in 5/32 (16%) people taking naproxen; four had stomach pain and dyspepsia, and one withdrew from the trial because of severe stomach pain.[37] One RCT comparing naproxen versus ergotamine found that vomiting was more frequent with ergotamine (10% with naproxen *v* 34% with ergotamine; P = 0.0083), and more people taking ergotamine withdrew because of severe symptoms (diarrhoea, vomiting, dizziness, nausea, shivering, and sweating) compared with those taking naproxen (2% with naproxen *v* 8% with ergotamine).[41] In another RCT, more people taking naproxen versus ergotamine discontinued medication (6/19 [32%] with naproxen *v* 2/17 [12%] with ergotamine).[40] One RCT found that more people taking ergotamine versus naproxen had severe adverse effects (1/48 [2%] with naproxen *v* 8/48 [17%] with ergotamine), and two people taking ergotamine withdrew from the study.[52] See non-steroidal anti-inflammatory drugs, p 1700.

Comment: None of the RCTs used the International Headache Society criteria (see glossary, p 1837) to identify cases.

OPTION TOLFENAMIC ACID

RCTs found limited evidence that tolfenamic acid improved duration and severity of headache compared with placebo. RCTs found no significant difference in symptom relief between tolfenamic acid and sumatriptan or paracetamol.

Benefits: We found no systematic review. **Versus placebo or sumatriptan:** One RCT (141 people, 289 migraine attacks) compared three treatments: tolfenamic acid 200 mg, sumatriptan 100 mg, and placebo.[42] The trial found that tolfenamic acid significantly increased headache relief (see glossary, p 1837) compared with placebo (AR 77% with tolfenamic acid *v* 29% with placebo; RR 2.6, 95% CI 1.5 to 4.2). However, it found no significant difference between tolfenamic acid and sumatriptan. The use of rescue medication (see glossary, p 1838) was not significantly different between any of the three arms. **Versus placebo or aspirin or ergotamine:** One crossover RCT (20 women with common or classic migraine, 160 migraines) compared tolfenamic acid

200 mg, aspirin 500 mg, and ergotamine 1 mg versus placebo.[43] The RCT found that tolfenamic acid significantly reduced the duration of attacks compared with placebo ($P < 0.001$; time of evaluation not reported). The mean duration of attack was shortest with tolfenamic acid compared with the other treatments, but this was not significantly shorter than the mean duration of attack with the other drugs combined (P values not reported). The need for rescue medication after 2 hours was not significantly different. **Versus paracetamol:** One RCT (149 people with common or classic migraine) compared tolfenamic acid 400 mg versus paracetamol 1000 mg.[44] It found no significant difference between treatments in headache intensity (see glossary, p 1837), adverse effects, strength, effect duration, or need for additional medication after 3 hours. **Combination preparations:** One crossover RCT (49 people with common or classic migraine, 482 migraines) compared tolfenamic acid alone or in combination with either caffeine or metoclopramide versus placebo.[45] The trial found that tolfenamic acid, either alone or in combination, significantly reduced headache intensity (measured on a scale of no, slight, moderate, or severe symptoms) compared with placebo. All combinations of tolfenamic acid significantly reduced the need for rescue medication compared with placebo ($P < 0.01$).

Harms: In one RCT comparing tolfenamic acid versus sumatriptan, the frequency of adverse effects was similar (30% *v* 41%).[41] See non-steroidal anti-inflammatory drugs, p 1700.

Comment: None.

OPTION ERGOTAMINE

One systematic review found limited evidence from four RCTs that ergotamine (with or without caffeine) improved headache relief compared with placebo. One overview of harms suggested that ergotamine increased nausea and vomiting compared with placebo. RCTs have found that ergotamine (or its derivatives, with or without caffeine and cyclizine) is less effective for migraine symptoms than sumatriptan. They found limited evidence that it was less effective than naproxen. RCTs found that ergotamine plus caffeine reduced headache relief and increased nausea and vomiting at 2 hours compared with oral lysine acetylsalicylate plus metoclopramide and rizatriptan.

Benefits: **Versus placebo:** We found one systematic review (search date 1991, 7 RCTs, 588 people).[46] Ergotamine was given orally at doses between 1 and 6 mg. Ergotamine was given alone in three RCTs, combined with caffeine in three RCTs, and combined with alkaloids and barbiturates in one RCT. The RCT of ergotamine plus alkaloids plus barbiturates was not evaluable. None of the trials used International Headache Society criteria (see glossary, p 1837) for participant inclusion, and defined responders according to a variety of 3 point to 10 point scales. Two RCTs identified by the review found that ergotamine alone significantly increased headache relief (see glossary, p 1837) compared with placebo ($P < 0.01$ in 1 RCT; reported as "significant" in the other RCT; P value not reported) and

one RCT found that ergotamine alone significantly reduced the duration of attacks compared with placebo ($P < 0.001$). Two RCTs identified by the review found a similar use of rescue medication (see glossary, p 1838) with ergotamine alone and with placebo (P value not reported; no further data reported). Two RCTs identified by the review measuring nausea or vomiting associated with migraine found similar results with ergotamine alone and placebo (P value not reported). One RCT identified by the review found that ergotamine plus caffeine significantly increased headache relief (reported as "significant"; P value not reported) compared with placebo, but another RCT found no significant difference (P value not reported). The RCTs comparing ergotamine plus caffeine versus placebo did not assess duration of attack. Two RCTs identified by the review found that ergotamine plus caffeine significantly reduced need for rescue medication ($P < 0.05$ in 1 RCT; reported as "significant" in the other, P value not reported). Two RCTs identified by the review measuring nausea or vomiting found that placebo reduced these symptoms compared with ergotamine plus caffeine (no statistical analysis reported). **Versus sumatriptan:** One RCT (580 people) compared oral ergotamine 2 mg plus oral caffeine 100 mg with oral sumatriptan 100 mg.[47] The trial found that ergotamine plus caffeine significantly reduced headache relief compared with sumatriptan (AR 48% with ergotamine plus caffeine *v* 66% with sumatriptan; RR 0.73, 95% CI 0.62 to 0.85; $P < 0.001$). Significantly more people required rescue medication with ergotamine plus caffeine than with sumatriptan (AR 44% with ergotamine plus caffeine *v* 24% with sumatriptan; RR 1.82, 95% CI 1.38 to 2.39). A second RCT (crossover design; 368 people treating 2 attacks) compared dihydroergotamine nasal spray (1 or 2 mg) with sumatriptan nasal spray (20 mg).[48] It found that sumatriptan significantly increased headache relief at 1 and 2 hours, and significantly reduced nausea at 1 hour compared with dihydroergotamine (headache relief at 1 hour: 53% with sumatriptan *v* 41% with dihydroergotamine; $P < 0.001$; headache relief at 2 hours: $P = 0.003$; relief of nausea at 1 hour: 64% with sumatriptan *v* 40% with dihydroergotamine; $P = 0.006$). However, the RCT found no significant differences between treatments with respect to relief from vomiting, photophobia, or phonophobia. **Versus eletriptan:** See benefits of eletriptan, p 1828. **Versus rizatriptan:** See benefits of rizatriptan, p 1831. **Plus metoclopramide:** One RCT (24 women with common or classic migraine, 176 migraines) found no significant difference between ergotamine alone and ergotamine plus metoclopramide in headache intensity (see glossary, p 1837) (measured on a 3 point scale as more than usual, usual, or less than usual) or need for rescue medication.[49] **Versus naproxen:** See benefits of naproxen, p 1823. **Plus caffeine versus salicylates:** One RCT (250 people randomised, 227 in efficacy analysis) found that lysine acetylsalicylate (L-ASA) 1620 mg plus metoclopramide 10 mg significantly increased headache relief compared with ergotamine 2 mg plus caffeine 200 mg (86/112 [77%] with L-ASA plus metoclopramide *v* 70/115 [61%] with ergotamine plus caffeine; $P = 0.01$).[25] It found that L-ASA plus

metoclopramide significantly reduced nausea and vomiting compared with ergotamine plus caffeine after 2 hours (people free from nausea or vomiting: 73/112 [65%] with L-ASA plus metoclopramide *v* 46/115 [40%] with ergotamine plus caffeine; P = 0.001).

Harms:

Versus placebo: In the systematic review comparing ergotamine versus placebo, two RCTs measuring nausea and vomiting found that ergotamine alone increased nausea and vomiting compared with placebo (no statistical analysis reported), and two RCTs found that ergotamine plus caffeine increased nausea and vomiting compared with placebo (no statistical analysis conducted).[46] We found one overview of the safety of dihydroergotamine mesylate (DHE) and ergotamine tartrate.[50] This overview identified two trials (24 and 311 people), which found that adverse effects with intramuscular DHE occurred in fewer than 10% of people (with leg cramps and pain at the injection site being most common) and that harms resolved within 1 hour. Three RCTs in the overview found that nausea and vomiting were the most common adverse effects, which subsided within 15 minutes. In another open trial (300 people), 32% of people taking DHE complained of nausea. Post-marketing surveillance studies have reported ischaemic complications, nausea, vomiting, seizures, cardiac and non-cardiac vascular disorders such as vasospasm and infarction, liver abnormalities, leg pain, chest pain, hypertensive crisis, injection site reactions, head and shoulder pain, and paraesthesia. Treatment related phenomena were reported in fewer than 4% of people receiving intranasal DHE. A bitter or unpleasant taste was reported by 2%. Dizziness and muscle pain were reported by less than 1%. Discontinuation of treatment occurred in 1% of people included in the RCTs. Worsening of baseline nausea or vomiting was suggested in 5/7 RCTs comparing acute administration of ergotamine tartrate versus placebo. Single case reports of less common adverse effects include abdominal discomfort, numbness or tingling of fingers or toes, ischaemic complications, swollen fingers, and leg cramps. With chronic use in excessive doses, ischaemic neuropathy, anorectal ulcers following suppository use, habituation, and overuse headaches have been reported.[50] **Versus sumatriptan:** In the RCT comparing sumatriptan versus dihydroergotamine nasal sprays, the incidence of adverse events was similar (about 10%) in both treatment groups after the first dose. The most common were disturbance of taste after sumatriptan, and nasal or sinus symptoms such as congestion, irritation, and rhinitis after dihydroergotamine. These were reported as being mild and self limiting.[48] **Plus caffeine versus salicylates:** One RCT found no significant difference in the proportion of people reporting at least one adverse event between L-ASA 1620 mg plus metoclopramide 10 mg and ergotamine 2 mg plus caffeine 200 mg (17% with L-ASA plus metoclopramide *v* 23% with ergotamine plus caffeine).[25] It found that the most common adverse events with the L-ASA regimen were somnolence (3.2%), dizziness (1.6%), and dry mouth (1.6%) and that abdominal pain (6.65), malaise (3.3%), anxiety (2.5%), and nervousness (1.7%) were the most common adverse events with the ergotamine regimen.

Comment:

None.

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OPTION **ELETRIPTAN**

One systematic review and subsequent RCTs have found that eletriptan increases headache relief at 2 hours compared with placebo. One systematic review and subsequent RCTs have found that eletriptan 40 and 80 mg increases headache relief at 2 hours compared with sumatriptan 50 and 100 mg. One RCT has found that eletriptan 40 and 80 mg increases headache relief at 2 hours compared with ergotamine plus caffeine.

Benefits:

Versus placebo: We found one systematic review (search date 2000, 8 RCTs, 5370 people)[51] and six subsequent RCTs.[52–57] The review found that all doses of eletriptan significantly increased headache relief (see glossary, p 1837) compared with placebo at 2 hours (eletriptan 20 mg, 499 people; eletriptan 40 mg, 1870 people; eletriptan 80 mg, 1393 people; total placebo groups 1113 people; AR for 20 mg: 48.9%; for 40 mg: 60.2%; for 80 mg: 65.8%; AR for placebo about 25%; ARR for 80 mg *v* placebo 42%, 95% CI 36% to 48%; for 40 mg *v* placebo 35.2%, 95% CI 29.8% to 40.7%). All six subsequent RCTs found that eletriptan significantly improved headache relief compared with placebo (See table A on web extra).[52–57] **Versus sumatriptan:** We found one systematic review[51] and two subsequent RCTs.[52,54] The review (search date 2000, 2 RCTs) found that eletriptan 40 and 80 mg significantly increased headache relief at 2 hours compared with sumatriptan 100 mg. It found no significant difference between eletriptan 20 mg and sumatriptan 100 mg (ARI for complete headache relief: eletriptan 80 mg: 18%, 95% CI 9% to 26%; eletriptan 40 mg: 11%, 95% CI 2% to 19%; eletriptan 20 mg: −1%, 95% CI −13% to +12%).[51] It found that eletriptan 40 and 80 mg significantly increased headache relief at 2 hours compared with sumatriptan 50 mg (ARI for eletriptan 80 mg: 15%, 95% CI 8% to 23%; eletriptan 40 mg: 10%, 95% CI 3% to 18%). The first subsequent RCT (1008 people) compared two doses of eletriptan (40 and 80 mg), two doses of sumatriptan (50 and 100 mg), and placebo.[52] It found that both doses of eletriptan significantly increased headache relief compared with sumatriptan at 2 hours (AR 108/169 [64%] with eletriptan 40 mg *v* 107/160 [67%] with eletriptan 80 mg *v* 88/176 [50%] with sumatriptan 50 mg *v* 85/160 [53%] with sumatriptan 100 mg; $P < 0.01$ for either dose eletriptan *v* sumatriptan 50 mg; $P < 0.05$ for either dose eletriptan *v* sumatriptan 100 mg). The second subsequent RCT (2072 people) compared three treatments: eletriptan 40 mg, sumatriptan 100 mg, and placebo.[54] It found that that eletriptan 40 mg significantly increased headache relief compared with sumatriptan 100 mg at 2 hours (67% with eletriptan *v* 59% with sumatriptan; $P < 0.001$). It found that eletriptan significantly reduced nausea compared with sumatriptan 100 mg at 2 hours (nausea absent: 74% with eletriptan *v* 67% with sumatriptan; $P < 0.01$). **Versus ergotamine plus caffeine:** We found one RCT (733 people treated included in the systematic review[51]) that compared two doses of eletriptan (40 and 80 mg), ergotamine plus caffeine, and placebo. It found that both doses of

eletriptan significantly increased headache relief and reduced nausea at 2 hours compared with ergotamine plus caffeine (headache relief: 111/206 [54%] with eletriptan 40 mg *v* 142/209 [68%] with eletriptan 80 mg *v* 65/197 [33%] with ergotamine plus caffeine; $P < 0.05$; nausea: results presented graphically; $P \leq 0.0001$ for both comparisons).[51]

Harms:

Versus placebo: We found one systematic review (search date 2000)[51] and four subsequent RCTs[54–57] that reported harms. The review found that higher doses of eletriptan 40 and 80 mg significantly increased any adverse event and central nervous system (CNS) adverse events (see glossary, p 1837) compared with placebo. It found no significant difference in adverse event rates with eletriptan 20 mg (ARI compared with placebo for any adverse event: 20 mg +1.9%, 95% CI −15.5% to +19.3%; 40 mg 7.3%, 95% CI 2.7% to 11.8%; 80 mg 18.9%, 95% CI 11.2% to 26.6%; CNS events: 20 mg +2.6%, 95% CI −6.6% to +11.7%; 40 mg 7.5%, 95% CI 4.5% to 10.6%; 80 mg 14.6%, 95% CI 10.2% to 19.0%). It found that 80 mg eletriptan significantly increased chest symptoms compared with placebo. It found no significant difference with 40 and 20 mg eletriptan (ARR compared with placebo, 20 mg −0.3%, 95% CI −3.1% to +2.6%; 40 mg +0.9%, 95% CI −0.2% to +2.0%; 80 mg 2.6%, 95% CI 0.6% to 4.5%).[51] The first subsequent RCT (2072 people analysed) found similar rates of adverse events between eletriptan 40 and 80 mg and placebo (about 30% in each group, P value not reported).[54] The second subsequent RCT (309 people analysed) found that eletriptan 20, 40, and 80 mg increased adverse events compared with placebo (16.3% with eletriptan 20 mg *v* 62.5% with eletriptan 40 mg *v* 45.5% with eletriptan 80 mg *v* 15.5% with placebo; P value not reported).[55] The most common adverse events were asthenia, nausea, and somnolence (asthenia: 1.3% with eletriptan 20 mg *v* 2.5% with eletriptan 40 mg *v* 11.7% with eletriptan 80 mg *v* 1.2% with placebo; nausea: 3.8% with eletriptan 20 mg *v* 7.5% with eletriptan 40 mg *v* 10.4% with eletriptan 80 mg *v* 2.4% with placebo; somnolence: 6.3% with eletriptan 20 mg *v* 10.0% with eletriptan 40 mg *v* 16.9% with eletriptan 80 mg *v* 3.6% with placebo, P value not reported).The third subsequent RCT found that eletriptan 40 and 80 mg increased nausea, chest symptoms, and asthenia compared with placebo (nausea: 5% with eletriptan 40 mg *v* 11% with eletriptan 80 mg *v* 8% with placebo; chest symptoms: 4% with eletriptan 40 mg *v* 5% with eletriptan 80 mg *v* 0% with placebo; asthenia: 5% with eletriptan 40 mg *v* 12% with eletriptan 80 mg *v* 2% with placebo, P value not reported).[56] The fourth subsequent RCT found that the most common adverse event was somnolence (2.8% with eletriptan 20 mg *v* 7.1% with eletriptan 40 mg *v* 8.7% with eletriptan 80 mg *v* 4.5% with placebo, P value not reported).[57] Other common adverse events with higher doses of eletriptan were asthenia and dizziness (asthenia: 3.1% with eletriptan 20 mg *v* 3.4% with eletriptan 40 mg *v* 7.1% with eletriptan 80 mg *v* 2.7% with placebo; dizziness: 2.8% with eletriptan 20 mg *v* 5.1% with eletriptan 40 mg *v* 6.1% with eletriptan 80 mg *v* 3.1% with placebo, P value not reported). **Versus sumatriptan:** The systematic review (search date 2000, 2 RCTs) found no significant difference between eletriptan 40 mg and sumatriptan 100 mg in adverse events or CNS

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related events (ARI, any event: 0%, 95% CI −11% to +11%; CNS events: −3%, 95% CI −13% to +8%).[51] It found that sumatriptan 50 mg significantly reduced adverse events and CNS related events compared with eletriptan 40 mg (ARR, any event: 8%, 95% CI 1% to 15%; CNS events: 8%, 95% CI 2% to 13%).[51] One subsequent RCT found similar rates of adverse events with eletriptan 40 mg and with sumatriptan 100 mg (31% with eletriptan *v* 37% with sumatriptan).[54] **Versus ergotamine plus caffeine:** One RCT (733 people treated) that compared two doses of eletriptan (40 and 80 mg), ergotamine 1 mg plus caffeine 100 mg, and placebo found that the most common adverse events were nausea and asthenia (nausea: 5% with eletriptan 40 mg *v* 10% with eletriptan 80 mg *v* 7% with ergotamine plus caffeine; asthenia: 4% with eletriptan 40 mg *v* 10% with eletriptan 80 mg *v* 3% with ergotamine plus caffeine, P value not reported).[51]

Comment: None.

OPTION NARATRIPTAN

One systematic review and subsequent RCTs have found that naratriptan increases headache relief at 2 hours compared with placebo. One systematic review has found that sumatriptan 100 mg increases headache relief at 2 hours compared with naratriptan 2.5 mg. However, one subsequent RCT found no significant difference in headache recurrence. One RCT found no significant difference between naratriptan 2.5 mg and zolmitriptan 2.5 mg in headache relief at 4 hours. One RCT identified by a systematic review found that naratriptan reduced headache relief at 2 hours compared with rizatriptan.

Benefits: **Versus placebo:** We found one systematic review (search date 2000, 5 RCTs, 1077 people)[51] and two subsequent RCTs.[58,59] The review found that naratriptan significantly increased headache relief (see glossary, p 1837) compared with placebo (ARI 22.2%, 95% CI 16.9% to 27.5%).[51] The first subsequent RCT (643 people) found that naratriptan 2.5 mg or sumatriptan 100 mg significantly increased headache relief at 4 hours compared with placebo (AR 63% with naratriptan *v* 80% with sumatriptan *v* 31% with placebo; $P < 0.05$ for either drug compared with placebo).[58] In the second subsequent RCT a subgroup of 206 people with a poor response to sumatriptan 50 mg in a first attack were randomised 1 week later to either naratriptan 2.5 mg orally or placebo.[59] Naratriptan significantly increased headache relief at 2 hours (AR 25% with naratriptan *v* 10% with placebo; RR 2.5, 95% CI 1.3 to 4.7) and at 4 hours (AR 41% with naratriptan *v* 19% with placebo; RR 2.2, 95% CI 1.4 to 3.5) compared with placebo. **Versus sumatriptan:** We found one systematic review (search date 2000, 2 RCTs, 480 people)[51] and one subsequent RCT.[60] The review found that sumatriptan 100 mg significantly increased headache relief at 4 hours compared with naratriptan 2.5 mg (AR not reported; ARI: 8%, 95% CI 0% to 16%).[51] The subsequent RCT comparing naratriptan 2.5 mg orally with sumatriptan 100 mg orally found no significant difference in headache recurrence (see glossary, p 1837).[60] **Versus zolmitriptan:** We found one systematic

review (search date 2000, 1 RCT, 179 people).[51] It found no significant difference between naratriptan 2.5 mg and zolmitriptan 2.5 mg in headache relief at 4 hours (difference: +1%, 95% CI −15% to +17%). **Versus rizatriptan:** See benefits of rizatriptan, p 1831.

Harms: **Versus placebo:** The systematic review found no significant difference in overall adverse events, central nervous system (CNS) adverse events, and chest related adverse events (see glossary, p 1837) between naratriptan 2.5 mg and placebo (ARI for naratriptan *v* placebo; any event: +2.4%, 95% CI −2.2% to +7.0%; CNS events: +1.9%, 95% CI −12.2% to +5.0%; chest symptoms: +0.4%, 95% CI −0.8% to +1.6).[51] One subsequent RCT found similar adverse effects with naratriptan 2.5 mg orally and placebo (21% with naratriptan *v* 23% with placebo; significance not reported).[58] **Versus sumatriptan:** The systematic review (search date 2000, 2 RCTs) found that sumatriptan 100 mg significantly increased adverse events compared with naratriptan 2.5 mg (difference: 11.3%, 95% CI 1% to 22.5%).[51] **Versus zolmitriptan:** The systematic review (search date 2000, 1 RCT) found that naratriptan 2.5 mg significantly reduced adverse events compared with zolmitriptan 2.5 mg (difference: −23%, 95% CI −37% to −8%).[51] **Versus rizatriptan:** See harms of rizatriptan, p 1832.

Comment: Naratriptan or a different triptan in a second attack may be beneficial in people responding poorly to sumatriptan in a first attack, but this requires confirmation in further RCTs.

OPTION RIZATRIPTAN

One systematic review and subsequent RCTs have found that rizatriptan improves headache relief compared with placebo. Two RCTs found no significant difference between rizatriptan and zolmitriptan in headache relief at 2 hours. One RCT identified by a systematic review found that rizatriptan increased headache relief at 2 hours compared with naratriptan. One RCT found that rizatriptan increased headache relief and reduced nausea and vomiting at 2 hours compared with ergotamine plus caffeine.

Benefits: **Versus placebo:** We found one systematic review (search date 2000, 12 RCTs, 6395 people)[51] and one subsequent RCT.[61] The systematic review found that rizatriptan significantly increased headache relief (see glossary, p 1837) at 2 hours compared with placebo (AR: 62.4% with rizatriptan 5 mg *v* 68.6% with rizatriptan 10 mg *v* about 34% with placebo; ARI compared with placebo presented graphically: about 28% with rizatriptan 5 mg *v* 35% with rizatriptan 10 mg). The subsequent RCT (727 people) compared three treatments: rizatriptan 10 mg, zolmitriptan 2.5 mg, and placebo.[61] It found that rizatriptan significantly increased headache relief compared with placebo (AR 71% with rizatriptan *v* 30% with placebo; $P < 0.05$).[61] **Versus zolmitriptan:** We found one systematic review (search date 2000, 1 RCT, 435 people)[51] and one subsequent RCT.[61] The systematic review found no significant difference between rizatriptan 10 mg and zolmitriptan 2.5 mg in headache relief at 2 hours (difference: +4%, 95% CI −4% to

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+11%).[51] The subsequent RCT (727 people) comparing rizatriptan 10 mg, zolmitriptan 2.5 mg, and placebo found no significant difference between rizatriptan and zolmitriptan in headache relief (AR 71% with rizatriptan *v* 67% with zolmitriptan; P = 0.23).[61] **Versus naratriptan:** One systematic review (search date 2000; 1 RCT 522 people) found that rizatriptan 10 mg significantly increased headache relief at 2 hours compared with naratriptan 2.5 mg (ARI 20%, 95% CI 11% to 30%).[51] **Versus ergotamine:** One RCT (439 people) compared oral rizatriptan 10 mg with ergotamine 2 mg plus caffeine 100 mg for the first migraine attack with the other treatment for a second attack.[62] It found that rizatriptan significantly increased headache relief and reduced nausea and vomiting at 2 hours compared with ergotamine plus caffeine (headache relief: 75.9% with rizatriptan *v* 47.3% with ergotamine plus caffeine; P ≤ 0.001; no nausea: 82.7% with rizatriptan *v* 56.2% with ergotamine plus caffeine; P ≤ 0.001; no vomiting: 96.2% with rizatriptan *v* 89.5% with ergotamine plus caffeine; P ≤ 0.001).

Harms: **Versus placebo:** We found one meta-analysis (search date 2000, 1963 people given rizatriptan 5 mg, 2783 people given rizatriptan 10 mg, and 1649 given placebo) that used individual patient data from published and unpublished RCTs.[51] It found that rizatriptan (5 and 10 mg) significantly increased overall and chest related adverse events (see glossary, p 1837) compared with placebo (placebo subtracted events: any event 7.9%, 95% CI 4.7% to 11.1% with rizatriptan 5 mg and 13.5%, 95% CI 10.6% to 16.3% with 10 mg rizatriptan; CNS events: 6.1%, 95% CI 3.2% to 9.0% with rizatriptan 5 mg and 9.4%, 95% CI 7.2% to 11.6% with rizatriptan 10 mg).[51] It found no significant difference in chest related adverse events between rizatriptan 5 mg and placebo but found that rizatriptan 10 mg significantly increased chest related adverse events compared with placebo (placebo subtracted chest symptoms: +0.9%, 95% CI −0.04 to +1.8 with rizatriptan 5 mg and 1.5%, 95% CI 0.8% to 2.3% with rizatriptan 10 mg). **Versus zolmitriptan:** The meta-analysis (search date 2000, 1 RCT) found no significant difference in adverse events between rizatriptan 10 mg and zolmitriptan 2.5 mg (difference: −8%, 95% CI −15% to 0%).[51] **Versus naratriptan:** The meta-analysis (search date 2000, 1 RCT) found that rizatriptan 10 mg significantly increased adverse events compared with naratriptan 2.5 mg (difference: 10%, 95% CI 1% to 19%).[51] **Versus ergotamine:** One RCT comparing rizatriptan 10 mg with ergotamine 2 mg plus caffeine 100 mg found no significant difference in adverse events (35.4% with rizatriptan *v* 34.5% with ergotamine plus caffeine).[62] The most common adverse events were dizziness, nausea, and somnolence (dizziness: 6.7% with rizatriptan *v* 5.3% with ergotamine; nausea: 4.2% with rizatriptan *v* 8.5% with ergotamine; somnolence: 5.5% with rizatriptan *v* 2.3% with ergotamine, P values not reported).

Comment: None.

OPTION SUMATRIPTAN

Systematic reviews and subsequent RCTs have found that subcutaneous, oral, or intranasal sumatriptan increases headache relief compared with placebo. RCTs found no significant difference in headache relief between

sumatriptan and aspirin plus metoclopramide, tolfenamic acid, or zolmitriptan. RCTs have found that oral or nasal sumatriptan increases headache relief compared with oral or nasal ergotamine. One systematic review has found that sumatriptan 100 mg increases headache relief at 2 hours compared with naratriptan 2.5 mg. However, one subsequent RCT found no significant difference in headache recurrence. One systematic review and subsequent RCTs have found that eletriptan 40 and 80 mg increases headache relief at 2 hours compared with sumatriptan 50 and 100 mg.

Benefits:

Subcutaneous sumatriptan: We found one systematic review (search date 1997),[63] one additional RCT,[64] and one subsequent RCT.[65] The review found that subcutaneous sumatriptan 6 mg significantly increased headache relief (see glossary, p 1837) at 1 hour compared with placebo (12 RCTs, 3127 people; 69% with sumatriptan *v* 19% with placebo; RR 3.7, 95% CI 3.3 to 4.2).[63] One additional crossover RCT (246 people with up to 12 migraines) comparing subcutaneous sumatriptan 6 mg with usual headache treatment (49% combinations, 24% ergotamine, 19% non-steroidal anti-inflammatory drugs, and 7% dihydroergotamine) found that sumatriptan significantly improved headache relief (78% with sumatriptan *v* 34% with usual treatment; $P < 0.001$).[64] The subsequent RCT (200 people consisting of 50 white people and 150 non-white people) compared headache relief across multiple attacks.[65] It analysed results by ethnic group. It found that subcutaneous sumatriptan 6 mg significantly increased headache relief in non-white people and white people (non-white: 87% with sumatriptan *v* 37% with placebo; white: 87% with sumatriptan *v* 19% with placebo; sumatriptan *v* placebo $P < 0.001$ in either ethnic group). **Oral sumatriptan:** We found one systematic review (search date 2000, 11 RCTs, 3185 people),[51] one additional RCT[66] and two subsequent RCTs.[52,54] The review found that sumatriptan significantly increased headache relief at 2 hours compared with placebo (AR 56.0% with sumatriptan 25 mg *v* 62.7% with sumatriptan 50 mg *v* 59.0% with sumatriptan 100 mg *v* about 30% with placebo; ARI about 25% with sumatriptan 25 mg [presented graphically] *v* about 33% with sumatriptan 50 mg [presented graphically] *v* 29%, 95% CI 26% to 34% with sumatriptan 100 mg).[51] The additional RCT (495 people) found that oral sumatriptan 50 mg significantly increased the proportion of people with headache relief after 4 hours in people with one attack compared with placebo (62% with sumatriptan *v* 32% with placebo; $P < 0.001$).[66] The first subsequent RCT (1008 people randomised, 774 people treated) compared two doses of eletriptan (40 and 80 mg), two doses of sumatriptan (50 and 100 mg), and placebo.[52] At 2 hours it found that both doses of sumatriptan significantly increased headache relief compared with placebo (50% with sumatriptan 50 mg *v* 53% with sumatriptan 100 mg *v* 31% with placebo; $P < 0.01$ for either dose of sumatriptan *v* placebo). The second subsequent RCT (2072 people) compared three treatments: eletriptan 40 mg, sumatriptan 100 mg, and placebo.[54] It found that that sumatriptan 100 mg significantly increased headache relief at 2 hours compared with placebo (59% with sumatriptan 100 mg *v* 26% with placebo; $P < 0.0001$). It found that sumatriptan 100 mg significantly reduced nausea at 2 hours

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compared with placebo (nausea absent: 67% with sumatriptan 100 mg *v* 57% with placebo; P < 0.001). **Intranasal sumatriptan:** We found one review (search date 1997)[63] and three additional RCTs.[67–69] The review found that intranasal sumatriptan 20 mg significantly increased headache relief compared with placebo (6 RCTs, 1420 people; 61% with sumatriptan *v* 30% with placebo; RR 2.1, 95% CI 1.8 to 2.4).[63] The three additional RCTs (2475 people) found that intranasal sumatriptan significantly increased headache relief compared with placebo (60–64% with sumatriptan *v* 25–35% with placebo).[67–69] **Versus aspirin plus metoclopramide:** See benefits of salicylates, p 1820. **Versus tolfenamic acid:** See benefits of tolfenamic acid, p 1824. **Versus ergotamine:** See benefits of ergotamine, p 1825. **Versus naratriptan:** See benefits of naratriptan, p 1830. **Versus zolmitriptan:** See benefits of zolmitriptan, p 1835. **Versus eletriptan:** See benefits of eletriptan, p 1828. **Versus ergotamine derivatives:** See benefits of ergotamine, p 1825.

Harms: **Subcutaneous sumatriptan:** In one systematic review (search date 1997), 7/12 RCTs found that adverse effects were more common with subcutaneous sumatriptan 6 mg than with placebo (65% with sumatriptan *v* 32% with placebo; OR 4, 95% CI 3 to 5).[63] The subsequent RCT found that subcutaneous sumatriptan increased adverse events compared with placebo in both non-white and white people (non-white: 63% with sumatriptan *v* 30% with placebo; white: 63% with sumatriptan *v* 23% with placebo; P value not reported).[65] It found nine serious adverse events with sumatriptan compared with none with placebo (no details reported and number exposed was not clear). **Oral sumatriptan versus placebo:** The systematic review found that sumatriptan 25, 50, and 100 mg) significantly increased overall adverse events compared with placebo (ARI: any event 4.4%, 95% CI 0.1% to 8.8% with sumatriptan 25 mg; 7.8%, 95% CI 2.6% to 13.1% with sumatriptan 50 mg; and 13.2%, 95% CI 8.6% to 17.8% with sumatriptan 100 mg).[51] It found that the two higher doses of sumatriptan (50 and 100 mg) significantly increased central nervous system (CNS) adverse events and chest related adverse events (see glossary, p 1837) compared with placebo. However, it found no significant difference between low dose sumatriptan 25 mg and placebo (ARI; CNS events: +1.7%, 95% CI –1.2% to +4.7% with sumatriptan 25 mg; 3.7%, 95% CI 1.0% to 6.5% with sumatriptan 50 mg; 6.3%, 95% CI 3.2% to 9.5% with sumatriptan 100 mg; chest related events: +0.8%, 95% CI –1.0% to +2.6% with sumatriptan 25 mg; 1.9%, 95% CI 0.4% to 3.3% with sumatriptan 50 mg; 1.7%, 95% CI 0.8% to 2.5% with sumatriptan 100 mg). One subsequent RCT found similar rates of adverse effects between sumatriptan and placebo (37% with sumatriptan *v* 34% with placebo, P value not reported).[54]

Comment: There is a consensus that sumatriptan should not be used in people with ischaemic heart disease or concomitantly with ergotamine.

OPTION ZOLMITRIPTAN

One systematic review and two subsequent RCTs have found that oral zolmitriptan increases headache relief compared with placebo. One systematic review and two subsequent RCTs found no significant difference between zolmitriptan and sumatriptan in headache relief. One RCT found no significant difference in headache relief between aspirin plus metoclopramide and zolmitriptan. One RCT found no significant difference between naratriptan 2.5 mg and zolmitriptan 2.5 mg in headache relief at 4 hours.

Benefits:

Versus placebo: We found one systematic review (search date 2000, 9 RCTs , 4641 people)[51] and two subsequent RCTs.[70,71] The systematic review found that zolmitriptan significantly increased headache relief (see glossary, p 1837) at 2 hours compared with placebo (AR: 63.5% with zolmitriptan 2.5 mg *v* 62.8% with zolmitriptan 5 mg *v* about 30% with placebo; ARI: about 30% with zolmitriptan 2.5 mg *v* about 33% with zolmitriptan 5 mg; results presented graphically). The first subsequent RCT (289 people, 229 in analysis) compared three doses of zolmitriptan (1, 2.5, and 5 mg) versus placebo.[70] It found that zolmitriptan 2.5 mg significantly increased headache relief at 2 hours compared with placebo (53.3% with zolmitriptan 1 mg; 55.6% with zolmitriptan 2.5 mg; 65.4% with zolmitriptan 5 mg; 37.5% with placebo; P = 0.032 for zolmitriptan 2.5 mg *v* placebo, other P values not reported; analysis not by intention to treat). The open label second subsequent RCT (470 people) found that orally dispersible zolmitriptan 2.5 mg significantly increased headache relief at 2 hours compared with placebo (63% with zolmitriptan *v* 22% with placebo; OR 6.1, 95% CI 4.0 to 9.3).[71] It found that zolmitriptan reduced nausea at 2 hours compared with placebo, but the statistical significance was not reported (no nausea: 52% with zolmitriptan *v* 32% with placebo). **Versus sumatriptan:** We found one systematic review (search date 2000, 3 RCTs)[51] and two subsequent RCTs.[72,73] The review found no significant difference between zolmitriptan 2.5 and 5 mg and sumatriptan 25, 50, and 100 mg in headache relief at 2 hours (ARR for sumatriptan 100 mg *v* zolmitriptan 5 mg: +1%, 95% CI −4% to +6%; sumatriptan 50 mg *v* zolmitriptan 2.5 mg: +2%, 95% CI −6% to +9%; sumatriptan 50 mg *v* zolmitriptan 5 mg: +1%, 95% CI −4% to +6%; sumatriptan 25 mg *v* zolmitriptan 2.5 mg: −8%, 95% CI −16% to 0%; sumatriptan 25 mg *v* zolmitriptan 5 mg: −7%, 95% CI −15% to 0%).[51] In the first subsequent RCT (1522 people), up to six consecutive attacks were treated with zolmitriptan 2.5 mg (500 people, 2671 attacks), zolmitriptan 5 mg (514 people, 2744 attacks), or sumatriptan 50 mg (508 people, 2693 attacks).[72] The RCT found no significant difference among groups for headache relief at 2 hours (AR 62.9% with zolmitriptan 2.5 mg *v* 65.7% with zolmitriptan 5 mg zolmitriptan *v* 66.6% with sumatriptan 50 mg). The second subsequent RCT (1445 people) compared zolmitriptan 2.5–5 mg versus sumatriptan 25–50 mg.[73] The trial found no significant difference in headache relief between treatments at any dose. **Versus salicylates:** One RCT (666 people) found no significant difference between aspirin 900 mg plus metoclopramide 10 mg and zolmitriptan 2.5 mg in headache relief at 2 hours over three migraine

attacks. However, it found that zolmitriptan significantly increased the proportion of people who were pain free (see glossary, p 1838) at 2 hours (headache relief: 32.9% with salicylates *v* 33.4% with zolmitriptan; OR 1.06, 95% CI 0.77 to 1.47; pain free: 10.7% with zolmitriptan *v* 5.3% with salicylates; OR 2.19, 95% CI 1.23 to 4.03).[26] It found that rates of nausea were similar with both treatments but the statistical significance was not reported (about 30% in each group). **Stratified care versus step care:** One open label RCT (835 people) randomised people into three arms.[74] The first arm, named "stratified care", randomised people with low disability scores to aspirin 800–1000 mg plus metoclopramide 10 mg, and people with higher disability scores to zolmitriptan 2.5 mg. The second arm, named "step care", involved treating initial attacks with aspirin plus metoclopramide and then switching to zolmitriptan 2.5 mg for the remaining two to three attacks. The third arm involved "step care within attacks", whereby all attacks were initially treated with aspirin plus metoclopramide, and non-responders were given zolmitriptan after 2 hours. It found that stratified care significantly increased the proportion of people with headache relief compared with either of the step care groups (AR 53% with stratified care *v* 40% with step care *v* 36% with step care within attacks; RR stratified care *v* step care 1.3, 95% CI 1.1 to 1.7; stratified care *v* step care within attacks 1.4, 95% CI 1.2 to 1.7). **Versus naratriptan:** See benefits of naratriptan, p 1830.

Harms:

Versus placebo: The systematic review found that zolmitriptan 2.5 and 5 mg significantly increased overall adverse events, central nervous system (CNS) adverse events, and chest related adverse events (see glossary, p 1837) compared with placebo (ARI compared with placebo; any adverse event: 15.9%, 95% CI 9.6% to 22.1% with 2.5 mg *v* 24.5%, 95% CI 15.3% to 33.5% with 5 mg; CNS events: 9.9%, 95% CI 4.3% to 15.5% with 2.5 mg *v* 11.5%, 95% CI 6.1% to 16.8% with 5 mg; chest related events: 2.0%, 95% CI 0.7% to 3.3% with 2.5 mg *v* 2.9%, 95% CI 1.2% to 4.6% with 5 mg).[51] The first subsequent RCT (289 Japanese people) found that zolmitriptan 5 mg increased asthenia, hypoaesthesia, and abdominal pain compared with placebo (asthenia: 7.0% with zolmitriptan 5 mg *v* 1.6% with 2.5 mg *v* 1.7% with placebo; hypoaesthesia: 7.0% with zolmitriptan 5 mg *v* 1.6% with 2.5 mg *v* 0% with placebo; abdominal pain: 7.0% with zolmitriptan 5 mg *v* 1.6% with 2.5 mg *v* 1.7% with placebo, P values not reported).[70] The second subsequent RCT found that zolmitriptan increased asthenia, throat tightness, and somnolence compared with placebo (asthenia: 3.5% with zolmitriptan *v* 1.3% with placebo; throat tightness: 2.6% with zolmitriptan *v* 0% with placebo; somnolence: 3.0% with zolmitriptan *v* 1.7% with placebo, P values not reported).[71] **Versus sumatriptan:** The systematic review (search date 2000, 3 RCTs) found no significant difference in adverse events between zolmitriptan 5 mg and sumatriptan 50 or 100 mg (ARI for zolmitriptan 5 mg *v* sumatriptan 100 mg: –2%, 95% CI –8% to +4%; zolmitriptan 2.5 mg *v* sumatriptan 50 mg: 4%, 95% CI 0% to 8%; zolmitriptan 5 mg *v* sumatriptan 50 mg: –2%, 95% CI –6% to +2%).[51] However, it found that sumatriptan 25 mg significantly reduced adverse events compared with zolmitriptan 5 mg (ARR: 12%, 95% CI 6% to 18%). The first subsequent RCT comparing

zolmitriptan 2.5 and 5 mg with sumatriptan 50 mg found no significant difference in adverse events.[72] **Versus salicylates:** One RCT found that zolmitriptan increased adverse events compared with salicylates plus metoclopramide but found no difference between treatments in withdrawals due to adverse events (adverse events: 40.8% with zolmitriptan *v* 29.1% with salicylates plus metoclopramide, P value not reported; withdrawal due to adverse events: 0.9% with zolmitriptan *v* 1.5% with salicylates plus metoclopramide, P value not reported).[26] It found that zolmitriptan increased paraesthesia (4.3% with zolmitriptan *v* 1.5% with salicylates plus metoclopramide), dizziness (2.8% with zolmitriptan *v* 0.6% with salicylates plus metoclopramide), and tightness (3.7% with zolmitriptan *v* 0.6% with salicylates plus metoclopramide) and that salicylates plus metoclopramide increased abdominal pain (2.8% with zolmitriptan *v* 5.0% with salicylates plus metoclopramide) and diarrhoea (1.2% with zolmitriptan *v* 2.1% with salicylates plus metoclopramide).

Comment: None.

GLOSSARY

Central nervous system (CNS) adverse events Events associated with triptans, including asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, speech disorders, abnormal thinking, tremor, vertigo, and other focal neurological symptoms.

Chest related adverse events Events associated with triptans, including chest pressure, chest pain, radiating pain to the arms, other chest discomfort, heavy arms, shortness of breath, palpitations, and anxiety.

Headache intensity Mild: normal activity allowed. Moderate: disturbing, but not prohibiting normal activity; bed rest not necessary. Severe: normal activity discontinued; bed rest may be necessary.

Headache recurrence In responders, change in headache intensity (see above) from mild/none to moderate/severe within 24 hours of study medication initial dose.

Headache relief Change in headache intensity (see above) score from severe/moderate to mild/none.

International Headache Society criteria (1988) *Migraine without aura (common migraine)* is defined as five or more headache attacks lasting for 4–72 hours with accompanying symptoms of either nausea/vomiting and/or phonophobia and photophobia. Pain should comply with at least two of the following four characteristics: unilateral, throbbing, moderate to severe intensity, and increase with physical activity. For *migraine with aura (classic migraine)*, two or more headache attacks are required that comply with three of the following four characteristics: one or more fully reversible aura symptom indicating focal cerebral cortical and/or brainstem dysfunction; at least one aura symptom developing gradually over more than 4 minutes or two or more symptoms occurring in succession; no aura symptom should last more than 1 hour; and headache follows aura with a pain free (see below) interval of less than 60 minutes. In both migraine with and without aura, secondary causes of headache should be excluded; if any structural damage is found, then it should not explain headache characteristics. Less stringent criteria for migraine without aura can be used. In clinical practice, the so called borderline migraine can be diagnosed when one of the above criteria is not met. International Headache Society criteria were not developed with the intention of identifying potential responders to different medications.

Migraine headache

Major and minor adverse effect A major adverse effect is defined as death, serious illness, or any adverse effect of sufficient severity to cause withdrawal from the study. A minor adverse effect is defined as any adverse effect that does not fulfil the criteria for a major harm.

Migraine index Pain scale for migraine resulting from duration times intensity of migraine where intensity is classified as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Pain free Change in headache intensity (see above) score from severe/moderate to none.

Rescue medication Additional medications different to study medication permitted in non-responders, usually limited to the habitual medications a person uses to treat their migraine headache.

REFERENCES

1. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and face pain. *Cephalalgia* 1988;8:12–96.
2. Stewart W, Linet M, Celentano D, et al. Age and sex specific incidence rates of migraine with and without visual aura. *Am J Epidemiol* 1991;134:1111–1120.
3. O'Brien B, Goerre R, Streiner D. Prevalence of migraine headache in Canada: a population based survey. *Int J Epidemiol* 1994;23:1020–1026.
4. Pryse-Phillips W, Findlay H, Tugwell P, et al. A Canadian population survey on the clinical, epidemiological and societal impact of migraine and tension type headache. *Can J Neurol Sci* 1992;19:333–339.
5. Stewart W, Lipton R, Celentano D, et al. Prevalence of migraine headache in the United States. *JAMA* 1992;267:64–69.
6. Kryst S, Scherl E. A population based survey of social and personal impact of headache. *Headache* 1994;34:344–350.
7. Morillo L, Sanin L, Takeuchi Y, et al. Headache in Latin America: a multination population-based survey. *Neurology* 2001;56(suppl 3):A454.
8. Bank J, Marton S. Hungarian migraine epidemiology. *Headache* 2000;40:164–169.
9. Henry P, Michel P, Brochet B, et al. A nationwide survey of migraine in France: prevalence and clinical features. *Cephalalgia* 1992;12:229–237.
10. Rasmussen B, Jensen R, Schroll, et al. Epidemiology of headache in a general population: a prevalence study. *J Clin Epidemiol* 1991;44:1147–1157.
11. Steiner T, Stewart W, Kolodner K, et al. Epidemiology of migraine in England. *Cephalalgia* 1999;19:305.
12. Cheung RTF. Prevalence of migraine, tension type headache and other headaches in Hong Kong. *Headache* 2000;40:473–479.
13. Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia* 1997;17:15–22.
14. Stewart W, Staffa J, Lipton R, et al. Familial risk of migraine: a population based study. *Ann Neurol* 1997;41:166–172.
15. Chabriat H, Joire J, Danchot J, et al. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo-controlled study. *Cephalalgia* 2001;14:297–300.
16. Tfelt-Hansen P, Henry P, Mulder L, et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995;346:923–926.
17. Deiner H. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine: a double-blind, double-dummy, randomized, multicenter, parallel group study. The ASASUMAMIG Study Group. *Cephalalgia* 1999;19:581–588.
18. Limmroth V, May A, Diener H. Lysine-acetylsalicylic acid in acute migraine attacks. *Eur Neurol* 1999;41:88–93.
19. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. *Cephalalgia* 1984;4:107–111.
20. Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg (aspirin) in acute migraine attacks; a multicentre, randomized, double-blind, single dose, placebo-controlled parallel group study. *Cephalalgia* 2000;20:663–667.
21. MacGregor EA, Dowson A, Davies PTG. Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002;42:249–259.
22. Lipton R, Stewart W, Ryan RJ, et al. Efficacy and safety of paracetamol, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998;55:210–217.
23. Boureau F, Joubert JM, Lasserre V, et al. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. *Cephalalgia* 1994;14:156–161.
24. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus metoclopramide in the acute treatment of migraine. *Eur Neurol* 1992;32:177–184.
25. Titus F, Escamilla C, da Costa Palmeira MM, ET AL. A double-blind comparison of lysine acetylsalicylate plus metoclopramide vs ergotamine plus caffeine in migraine effects on nausea, vomiting and headache symptoms. *Clin Drug Invest* 2001;21:87–94.
26. Geraud G, Compagnon A, Rossi A. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *Eur Neurol* 2002;47:88–98.
27. Massiou H, Serrurier D, Lasserre O, et al. Effectiveness of oral diclofenac in the acute treatment of common migraine attacks: a double-blind study versus placebo. *Cephalalgia* 1991;11:59–63.

28. Dahlof C, Bjorkman R. Diclofenac-K (50 and 100 mg) and placebo in the acute treatment of migraine. *Cephalalgia* 1993;13:117–123.
29. Bigal ME, Bordini CA, Speciali JG. Intramuscular diclofenac in the acute treatment of migraine: a double-blind placebo controlled study. *Arq Neuropsiquiatr* 2002;60:410–415. [In Portuguese]
30. The Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of nonsteroidal anti-inflammatory drug, diclofenac-potassium in comparison to oral sumatriptan and placebo. *Cephalalgia* 1999;19:232–240.
31. Karachalios G, Fotiadou A, Chrisikos N, et al. Treatment of acute migraine attack with diclofenac sodium: a double blind study. *Headache* 1992;32:98–100.
32. Kellstein D, Lipton R, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. *Cephalalgia* 2000;20:233–243.
33. Kloster R, Nestvold K, Vilming S. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. *Cephalalgia* 1992;12:169–171.
34. Havanka-Kanniainen H. Treatment of acute migraine attack: ibuprofen and placebo compared. *Headache* 1989;29:507–509.
35. Codispoti JR, Prior MJ, Fu M, et al. Efficacy of non-prescription doses of ibuprofen in treating migraine headache. A randomized clinical trial. *Headache* 2001;41:665–679.
36. Sandrini G, Franchini S, Lanfranchi S, et al. Effectiveness of ibuprofen-arginine in the treatment of acute migraine attacks. *Int J Clin Pharmacol Res* 1998;18:145–150.
37. Andersson P, Hinge H, Johansen O, et al. Double-blind study of naproxen v placebo in the treatment of acute migraine attacks. *Cephalalgia* 1989;9:29–32.
38. Nestvold K, Kloster R, Partinen M, et al. Treatment of acute migraine attack: naproxen and placebo compared. *Cephalalgia* 1985;5:115–119.
39. Pradalier A, Rancurel G, Dordain G, et al. Acute migraine attack therapy: comparison of naproxen sodium and an ergotamine tartrate compound. *Cephalalgia* 1985;5:107–112.
40. Treves T, Streiffler M, Korczyn A. Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992;32:280–282.
41. Sargent J, Baumel B, Peters K, et al. Aborting a migraine attack: naproxen v ergotamine plus caffeine. *Headache* 1988;28:263–266.
42. Myllyla V, Havanka H, Herrala L, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache* 1998;38:201–207.
43. Hakkarainen H, Vapaatalo H, Gothoni G, et al. Tolfenamic acid is as effective as ergotamine during migraine attacks. *Lancet* 1979;2:326–328.
44. Norrelund N, Christiansen L, Plantener S. Tolfenamic acid versus paracetamol in migraine attacks. A double-blind study in general practice. *Ugeskr Laeger* 1989;151:2436–2438.
45. Tokola R, Kangasniemi P, Neuvonen P, et al. Tolfenamic acid, metoclopramide, caffeine and their combinations in the treatment of migraine attacks. *Cephalalgia* 1984;4:253–263.
46. Dahlof C. Placebo-controlled clinical trials with ergotamine in the acute treatment of migraine. *Cephalalgia* 1993;13:166–171. Search date 1991; primary sources Medline, Embase, and hand searches of reference lists.
47. Multinational Oral Sumatriptan Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. *Eur Neurol* 1991;31:314–322.
48. Bourea F, Kappos L, Schoenen J, et al. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract* 2000;54:281–286.
49. Hakkarainen H. Ergotamine vs. metoclopramide vs. their combination in acute migraine attacks. *Headache* 1982;22:10–12.
50. Lipton R. Ergotamine tartrate and dihydroergotamine mesylate: safety profiles. *Headache* 1997;37:S33–S41.
51. Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT_1 B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22:633–658. Search date: 2000; primary sources five pharmaceutical companies and systematic review of literature (no details). [Erratum in: *Cephalalgia* 2003;23:71]
52. Sandrini G, Farkkila M, Gurgess G, et al. Eletriptan versus sumatriptan: a double-blind, multiple migraine attack study. *Neurology* 2002;59:1210–1217.
53. Stark R, Dahlos C, Haughie S, et al. Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine: results of a phase III, multicentre, placebo controlled study across three attacks. *Cephalalgia* 2002;22:23–32.
54. Mathew NT, Schoenen J, Winner P, et al. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache* 2003;43:214–222.
55. Eletriptan Steering Committee in Japan. Efficacy and safety of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs. *Cephalalgia* 2002;22:416–423.
56. Färkkilä M, Olesen J, Dahlöf C, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia* 2003;23:463–471.
57. Sheftell F, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache* 2003;43:202–213.
58. Havanka H, Dahlof C, Pop P, et al. Efficacy of naratriptan tablets in the acute treatment of migraine: a dose-ranging study. *Clin Ther* 2000;22:970–980.
59. Stark S, Spierings E, McNeal S, et al. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. *Headache* 2000;40:513–520.
60. Gobel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. *Clin Ther* 2000;22:981–989.
61. Pascual J, Vega P, Deiner H-C, et al. Comparison of rizatriptan 10 mg vs. zolmitriptan 2.5 mg in the acute treatment of migraine. *Cephalalgia* 2000;20:455–461.
62. Christie S, Gobel H, Mateos V, et al. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol* 2003;49:20–29.
63. Tfelt-Hansen P. Efficacy and harms of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment: a systematic review based on number needed to treat. *Cephalalgia* 2001;18:532–538. Search date 1997; primary

sources Medline and hand searches of *Arch Neurol*, *Neurology*, *Headache*, and *Cephalalgia* from 1990.
64. Boureau F, Chazot G, Emile J, et al. Comparison of subcutaneous sumatriptan with usual acute treatments for migraine. French Sumatriptan Study Group. *Eur Neurol* 1995;35:264–269.
65. Burke-Ramirez P, Asgharnejad M, Webster C, et al. Efficacy and tolerability of subcutaneous sumatriptan for acute migraine: a comparison between ethnic groups. *Headache* 2001;41:873–882.
66. Savani N, Brautaset NJ, Reunanen M, et al. A double-blind placebo-controlled study assessing the efficacy and tolerability of 50 mg sumatriptan tablets in the acute treatment of migraine. Sumatriptan Tablets S2CM07 Study Group. *Int J Clin Pract Suppl* 1999;105:7–15.
67. Peikert A, Becker WJ, Ashford EA, et al. Sumatriptan nasal spray: a dose-ranging study in the acute treatment of migraine. *Eur J Neurol* 1999;6:43–49.
68. Diamond S, Elkind A, Jackson RT, et al. Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine. *Arch Fam Med* 1998;7:234–240.
69. Ryan R, Elkind A, Baker CC, et al. Sumatriptan nasal spray for the acute treatment of migraine. Results of two clinical studies. *Neurology* 1997;49:1225–1230.
70. Sakai F, Iwata M, Tashiro K, et al. Zolmitriptan is effective and well tolerated in Japanese patients with migraine: a dose–response study. *Cephalalgia* 2002;22:376–383.
71. Dowson AJ, MacGregor EA, Purdy RA, et al. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia* 2002;22:101–106.
72. Gruffyd-Jones K, Kies B, Middleton A, et al. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: a randomized, double-blind, international study. *Eur J Neurol* 2001;8:237–245.
73. Gallagher R, Dennidh G, Spierings E, et al. A comparative trial of zolmitriptan and sumatriptan for the acute oral treatment of migraine. *Headache* 2000;40:119–128.
74. Lipton RB, Stewart WF, Stone AM, et al. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) study: a randomized trial. *JAMA* 2000;284:2599–2605.

Luis E Morillo
Associate Professor
Javeriana University
Faculty of Medicine
Department of Neurosciences,
Neurology Unit and Clinical Epidemiology
and Biostatistics Unit
Bogota
Colombia

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